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Association of Parameters of Mineral Bone Disorder with Mortality in Patients on Hemodialysis according to Level of Residual Kidney Function

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Abstract

Background and objectives The relationship between mineral and bone disorders and survival according to residual kidney function status has not been previously studied in patients on hemodialysis. We hypothesized that residual kidney function, defined by renal urea clearance, modifies the association between mineral and bone disorder parameters and mortality.

Design, setting, participants, & measurements The associations of serum phosphorus, albumin-corrected calcium, intact parathyroid hormone, and alkaline phosphatase with all-cause mortality were examined across three strata (<1.5, 1.5 to <3.0, and ≥3.0 ml/min per 1.73 m²) of baseline residual renal urea clearance using Cox models adjusted for clinical characteristics and laboratory measurements in 35,114 incident hemodialysis patients from a large United States dialysis organization over the period of 2007–2011.

Results A total of 8102 (23%) patients died during the median follow-up of 1.3 years (interquartile range, 0.6–2.3 years). There was an incremental mortality risk across higher serum phosphorus concentrations, which was pronounced among patients with higher residual renal urea clearance ($P_{\text{interaction}}=0.001$). Lower concentrations of serum intact parathyroid hormone were associated with higher mortality among patients with low residual renal urea clearance (i.e., <1.5 ml/min per 1.73 m²), whereas higher concentrations showed a higher mortality risk among patients with greater residual renal urea clearance (i.e., ≥1.5 ml/min per 1.73 m²; $P_{\text{interaction}}<0.001$). Higher serum corrected total calcium and higher alkaline phosphatase concentrations consistently showed higher mortality risk ($P_{\text{trend}}<0.001$ for both) irrespective of residual renal urea clearance strata ($P_{\text{interaction}}=0.34$ and $P_{\text{interaction}}=0.53$, respectively).

Conclusions Residual kidney function modified the mortality risk associated with serum phosphorus and intact parathyroid hormone among incident hemodialysis patients. Future studies are needed to examine whether taking account for residual kidney function into the assessment of mortality risk associated with serum phosphorus and intact parathyroid hormone improves patient management and clinical outcomes in the hemodialysis population.

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Introduction

Mineral and bone disorder (MBD), characterized by abnormal serum concentrations of calcium, phosphorus, intact parathyroid hormone (PTH), and alkaline phosphatase (ALP), are a common complication in patients with CKD, especially in those with ESRD (1). The above MBD abnormalities may lead to high mortality risk due to adverse cardiovascular or infection-related pathways (2–5). However, those abnormalities may be attenuated in patients on hemodialysis with substantial residual kidney function (RKF) who maintain greater solute clearance (6). Preserved RKF also offers other clinical benefits, including lower ultrafiltration volume, less intradialytic hypotension, and lower prevalence of anemia as well as decreased progression rate of malnutrition,

inflammation, erythropoietin resistance, and ventricular hypertrophy (6–8). Therefore, the associations of such clinical parameters with mortality and the effect of interventions on patient survival may differ depending on RKF levels among patients on hemodialysis. Indeed, several studies have suggested that frequent hemodialysis is beneficial to those with little or no RKF but may be detrimental to those with substantial RKF (9–11).

However, few studies have taken RKF levels into account when evaluating associations between MBD markers and mortality in patients on hemodialysis, although up to 45% of patients in the United States initiate maintenance dialysis at eGFRs >10 ml/min per 1.73 m² (12,13). Hence, we hypothesized that RKF levels modify the associations of serum phosphorus,

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calcium, intact PTH, and ALP with all-cause mortality in patients on hemodialysis.

Materials and Methods

Patients

We retrospectively extracted, refined, and examined data from all incident hemodialysis patients who initiated treatment between 2007 and 2011 and were treated for ≥ 60 consecutive days in facilities operated by a large dialysis organization in the United States. Patients were followed up from their first dialysis date to December 31, 2011. Of the 133,162 incident ESRD patients who were treated with in-center thrice-weekly hemodialysis as their initial dialysis modality, we excluded 21,125 patients who were ever treated with other modalities; 3012 who had missing data on MBD parameters, such as serum phosphorus, calcium, intact PTH, or ALP, at baseline (*i.e.*, the first quarter or 91 days of dialysis); and 73,911 who had missing data on baseline residual renal urea clearance (rCL_{urea}) (Supplemental Figures 1). Our final study population consisted of 35,114 incident hemodialysis patients. This study was approved by the University of California Irvine Medical Center and the University of Washington with the exemption of obtaining written consent given the large sample size, anonymity of the patients studied, and noninvasive nature of the research.

Demographic, Clinical, and Laboratory Measures

Information on all-cause death, race/ethnicity, primary insurance, vascular access type, comorbidities, and laboratory variables were obtained from the electronic database of the dialysis provider.

Blood samples were drawn using uniform techniques in all dialysis clinics and transported to the central laboratory in Deland, Florida, typically within 24 hours. All laboratory values were measured by automated and standardized methods. Most laboratory values were measured monthly, including serum urea nitrogen, creatinine, albumin, calcium, phosphorus, and bicarbonate. Serum ferritin and intact PTH were measured at least quarterly. Hemoglobin was measured at least monthly in all patients and weekly to biweekly in most patients. Most blood samples were collected predialysis, with the exception of the postdialysis urea that was obtained to calculate urea kinetics.

We used rCL_{urea} as the index of RKF in all analyses. The average serum urea concentrations during collection were assumed to be 90% of the predialysis concentrations according to the approach by Daugirdas *et al.* (14), and thus, rCL_{urea} was calculated as follows:

$$rCL_{urea} (\text{ml/min}) = \frac{\text{urinary urea nitrogen (mg/dl)} \times \text{urinary volume (ml)}}{\text{collected time (min)} \times [0.9 \times \text{predialysis serum urea nitrogen (mg/dl)}]}$$

where serum urea nitrogen was obtained on the closest day within ± 28 days of urine collection. Urine collected time was reported as 1440 minutes in 98% of measurements, ranging from 720 to 2880 minutes. We then adjusted rCL_{urea} for body surface area and expressed it as milliliter per minute per 1.73 m^2 (15,16). Normalized protein catabolic rate (nPCR) was calculated accounting for rCL_{urea} (17,18).

To minimize measurement variability, averaged values of laboratory variables, including rCL_{urea} , during the first

patient-quarter (or the first 91 days of dialysis) within each patient served as baseline data and were used in all models.

Statistical Analyses

Differences in baseline characteristics between included versus excluded patients were compared by standardized differences (19,20). Patients were categorized into three groups according to baseline rCL_{urea} strata (<1.5 , 1.5 to <3.0 , and $\geq 3.0 \text{ ml/min per } 1.73 \text{ m}^2$), and associations of patient characteristics with rCL_{urea} categories were evaluated by nonparametric trend tests. The cutoff value of $3.0 \text{ ml/min per } 1.73 \text{ m}^2$ was selected on the basis of the definition of substantial RKF in the previous studies and guidelines (11,21,22). To evaluate trends across rCL_{urea} levels, we also used an additional cutoff point at $1.5 \text{ ml/min per } 1.73 \text{ m}^2$, so that all groups maintained reasonable sample sizes, even after being stratified by each MBD parameter. MBD parameters were treated as categorical variables, and their association with all-cause mortality was examined by Cox proportional hazard models.

For each analysis, we used hierarchical adjustment with three models as follows: (1) unadjusted models that included the *a priori*-defined categories of each one of the exposures (*i.e.*, phosphorus, uncorrected or albumin-corrected calcium, intact PTH, or ALP); (2) case mix-adjusted models that included the above variables plus age, sex, race/ethnicity, primary insurance, central venous catheter use, hypertension, diabetes, history of cardiovascular disease (*i.e.*, congestive heart failure, atherosclerotic heart disease, cerebrovascular disease, or other cardiovascular disease), rCL_{urea} , and single-pool Kt/V; and (3) case mix-plus malnutrition-inflammation cachexia syndrome (MICS)-adjusted models that included all covariates in the case mix model plus body mass index, nPCR, hemoglobin, serum albumin, creatinine, ferritin, and the use of medications, including vitamin D receptor activators (*i.e.*, calcitriol, paricalcitol, or doxercalciferol either oral or intravenous), calcium-containing phosphorus binders, and noncalcium-containing phosphorus binders (*i.e.*, sevelamar and lanthanum), as well as MBD parameters other than the exposure of interest (*i.e.*, phosphorus, uncorrected calcium, and natural log-transformed intact PTH and ALP).

We defined the fully adjusted model (*i.e.*, case mix-plus MICS-adjusted models) as the primary model. Hazard proportionality was confirmed by Schoenfeld residuals. Associations of MBD markers with mortality were also evaluated across strata of rCL_{urea} . Effect modification of the association between each MBD parameter and mortality by rCL_{urea} was evaluated by creation of interaction terms and use of the Wald test. We also categorized patients into a total of 12 or 15 groups according to combined baseline levels of rCL_{urea} and each MBD parameter and examined their associations with mortality. Consistent results were observed in sensitivity analyses using restricted cubic spline functions with four knots (Supplemental Figures 2–6) or excluding patients with $rCL_{urea} > 15 \text{ ml/min per } 1.73 \text{ m}^2$ (data not shown).

The frequency of missing data was low ($<1\%$ for most laboratory tests, except for nPCR [6%] and creatinine [4%]), and multiple imputation methods with five datasets were used in all regression analyses. Analyses were conducted

using STATA MP, version 13.1 (StataCorp, College Station, TX).

Results

Baseline Characteristics

The cohort included 35,114 incident hemodialysis patients, in whom the mean \pm SD age was 62 \pm 15 years old; there were 63% men, 55% non-Hispanic white, and 27% non-Hispanic black, and 59% of patients had diabetes. Mean or median serum baseline phosphorus, albumin-corrected calcium, intact PTH, and ALP levels were 5.0 \pm 1.1 mg/dl, 9.1 \pm 0.5 mg/dl, 312 (interquartile range [IQR], 201–477) pg/dl, and 84 (IQR, 67–110) U/L, respectively. The prevalence rates of patients with low (<1.5 ml/min per 1.73 m²), middle (1.5 to <3.0 ml/min per 1.73 m²), and high (\geq 3.0 ml/min per 1.73 m²) rCL_{urea} levels were 20%, 28%, and 52%, respectively. Median urine volume was 300 (IQR, 200–450), 600 (IQR, 500–900), and 1200 (IQR–850, 1675) ml/d in the low, middle, and high rCL_{urea} groups, respectively. Patients with greater rCL_{urea} tended to have higher albumin and uncorrected calcium levels and had lower creatinine, phosphorus, intact PTH, and ALP levels (Table 1). A total of 8102 (23%) patients died during the median follow-up of 1.3 years (IQR, 0.6–2.3 years), with an incidence of 15.0 deaths per 100 patient-years. The leading cause of death was cardiovascular disease (40%) followed by withdrawal from dialysis/uremia (10%), infection (7%), and malignancy (4%).

Compared with 76,923 excluded patients who lacked data on baseline rCL_{urea}, phosphorus, albumin-corrected calcium, intact PTH, or ALP, the 35,114 included patients were more likely to be men, non-Hispanic white, and vitamin D receptor activator users; had higher levels of body mass index, Kt/V, hemoglobin, and albumin; and had lower levels of ALP and ferritin (standardized difference >0.1) (Supplemental Table 1). Associations of these MBD parameters with all-cause mortality were found to be similar between included versus excluded patients in the fully adjusted models without adjustment for rCL_{urea} and nPCR, the missingness of which was the most common reason for exclusion (>95%) (Supplemental Figure 7).

Association of Phosphorus and All-Cause Mortality according to rCL_{urea} Strata

In the unadjusted model, higher serum phosphorus was associated with better survival. This association was attenuated in the case mix model and even reversed in the MICS model (fully adjusted model) across all rCL_{urea} strata (Figure 1, A–C). Fully-adjusted mortality risk associated with serum phosphorus was significantly modified by rCL_{urea} ($P_{\text{interaction}}=0.001$), in which the association of higher serum phosphorus with mortality was more pronounced across higher levels of rCL_{urea}: adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CIs) of the highest phosphorous group (\geq 7.0 mg/dl) versus the second lowest group (4.0 to <5.0 mg/dl) were 1.31 (95% CI, 1.05 to 1.64), 1.77 (95% CI, 1.45 to 2.17), and 1.93 (95% CI, 1.59 to 2.33) among patients in the low, middle, and high rCL_{urea} strata, respectively (Figure 1, A–C). When categorizing patients into 15 groups according to combined baseline levels of serum phosphorus and rCL_{urea} (reference: serum phosphorous =4.0–5.0 mg/dl and

rCL_{urea} \geq 3.0 ml/min per 1.73 m²), a trend toward lower mortality risk was observed across higher rCL_{urea} within given serum phosphorus categories <6.0 mg/dl ($P_{\text{trend}}<0.001$) but was not observed within the higher categories (Figure 1D).

Association of Calcium and All-Cause Mortality according to rCL_{urea} Strata

The overall mortality risk associated with higher albumin-corrected calcium was higher in all models ($P_{\text{trend}}\leq 0.002$ for all models). Compared with the middle corrected calcium group (*i.e.*, 8.8 to <9.2 mg/dl), aHR was 1.08 (95% CI, 1.01 to 1.16) in the highest group (*i.e.*, \geq 9.6 mg/dl) overall (Supplemental Figure 7B). The association between corrected calcium and mortality was not significantly modified by rCL_{urea} in the fully adjusted model ($P_{\text{interaction}}=0.34$), and the trend in the adjusted association between corrected calcium and mortality seemed consistent across rCL_{urea} strata (Figure 2, A–C). Higher rCL_{urea} was consistently associated with lower mortality risk across serum calcium categories in models evaluating 15 groups of combined rCL_{urea} and corrected calcium levels (reference: corrected calcium =8.8 to <9.2 mg/dl and rCL_{urea} \geq 3.0 ml/min per 1.73 m²; $P_{\text{trend}}<0.001$ for all) (Figure 2D). Consistent patterns were observed in the association between uncorrected calcium and mortality (Supplemental Figure 8).

Association of PTH and All-Cause Mortality according to rCL_{urea} Strata

Higher serum intact PTH levels were associated with lower risk of mortality in the unadjusted models across all three rCL_{urea} groups. In the fully adjusted model, this association was attenuated but still significant in the lowest rCL_{urea} group ($P=0.004$), but it reversed in the middle and highest rCL_{urea} groups ($P=0.05$ and $P<0.01$, respectively; $P_{\text{interaction}}<0.001$) (Figure 3, A–C). Compared with the second lowest PTH group (150 to <300 pg/ml), the aHRs of the lowest group (<150 pg/ml) were 1.05 (95% CI, 0.92 to 1.19), 0.94 (95% CI, 0.83 to 1.07), and 0.99 (95% CI, 0.90 to 1.09) among patients in the low, middle, and high rCL_{urea} groups, respectively, whereas the aHRs of the highest intact PTH group (\geq 600 pg/ml) versus the reference were 0.93 (95% CI, 0.79 to 1.09), 1.11 (95% CI, 0.96 to 1.29), and 1.12 (95% CI, 0.99 to 1.26) among patients in the low, middle, and high rCL_{urea} groups, respectively. Models using spline functions yielded consistent results (Supplemental Figure 5). When categorizing patients into 12 groups according to baseline levels of intact PTH and rCL_{urea}, the mortality risk in the high rCL_{urea} group versus the low rCL_{urea} group was attenuated to some extent in higher intact PTH levels but consistently lower across PTH categories (reference: intact PTH =150 to <300 pg/ml and rCL_{urea} \geq 3.0 ml/min per 1.73 m²) (Figure 3D).

Association of ALP and All-Cause Mortality according to rCL_{urea} Strata

Higher ALP was associated with higher mortality irrespective of adjustment models overall. Compared with the middle ALP group (*i.e.*, 60 to <80 IU/L), the highest group (*i.e.*, \geq 120 IU/L) was associated with higher mortality risk with aHR of 1.36 (95% CI, 1.28 to 1.45) (Supplemental

Table 1. Baseline characteristics of 35,114 incident hemodialysis patients stratified by baseline residual renal urea clearance

Characteristics	Total, n=35,114	rCL _{urea} , ml/min per 1.73 m ²			P _{trend} Value
		<1.5, n=7124	1.5 to <3.0, n=9899	≥3.0, n=18,091	
rCL _{urea} , ml/min per 1.73 m ²	3.08 (1.75–4.92)	0.93 (0.56–1.22)	2.24 (1.87–2.61)	4.84 (3.81–6.49)	<0.001
Age, yr	62±15	63±16	62±15	62±14	<0.001
Men, %	63	54	59	69	<0.001
Race, %					<0.001
Non-Hispanic white	55	50	52	58	<0.001
Non-Hispanic black	27	33	29	24	<0.001
Hispanic and other	18	17	18	18	0.06
Primary insurance, %					<0.001
Medicare	51	55	52	50	<0.001
Medicaid	6	7	7	6	0.001
Others	42	39	42	44	<0.001
Vascular access, %					<0.001
Central venous catheter	74	81	75	71	<0.001
AV fistula/graft	22	15	21	25	<0.001
Unknown	4	5	4	4	0.11
Comorbidities, %					
Diabetes	59	56	58	60	<0.001
Hypertension	51	54	52	48	<0.001
Congestive heart failure	38	40	39	37	<0.001
Atherosclerotic heart disease	14	14	14	14	0.34
Cerebrovascular	2	2	2	1	0.16
Other cardiovascular disease	15	16	15	15	0.10
Body mass index, kg/m ²	27.4 (23.6–32.6)	27.4 (23.4–33.1)	27.2 (23.5–32.5)	27.5 (23.8–32.6)	0.14
Single-pool Kt/V	1.57±0.37	1.42±0.27	1.49±0.28	1.68±0.40	<0.001
nPCR, g/kg per d	0.98±0.29	0.85±0.24	0.93±0.25	1.06±0.30	<0.001
Laboratory variables					
Hemoglobin, g/dl	11.2±1.1	11.0±1.1	11.2±1.1	11.4±1.1	<0.001
Albumin, g/dl	3.57±0.46	3.50±0.47	3.56±0.45	3.60±0.46	<0.001
Creatinine, mg/dl	5.8±2.3	6.8±2.8	6.3±2.4	5.2±1.9	<0.001
Uncorrected calcium, mg/dl	8.7±0.6	8.7±0.6	8.7±0.6	8.7±0.6	<0.001
Corrected calcium, mg/dl	9.1±0.5	9.1±0.6	9.1±0.6	9.1±0.5	0.12
Phosphorus, mg/dl	5.0±1.1	5.2±1.3	5.1±1.1	4.8±1.0	<0.001
Intact PTH, pg/ml	312 (201–477)	329 (206–520)	333 (216–509)	297 (192–445)	<0.001
Alkaline phosphatase, U/L	84 (67–110)	87 (69–117)	85 (67–111)	83 (66–107)	<0.001
Ferritin, ng/ml	268 (157–450)	306 (178–511)	267 (158–442)	256 (149–430)	<0.001
Medication use, %					
Vitamin D receptor activators	74	73	77	73	<0.01
Calcium-containing phosphorus binders	19	19	20	18	0.06
Sevelamar or lanthanum	17	19	18	16	<0.001

Values are expressed as mean±SD, median (interquartile range), or percentage appropriately. Conversion factors for units: albumin and hemoglobin in grams per deciliter to grams per liter, 10; creatinine in milligrams per deciliter to millimoles per liter, 88.4; calcium in milligrams per deciliter to millimoles per liter, 0.2495; and phosphorus in milligrams per deciliter to millimoles per liter, 0.3229. No conversion is necessary for ferritin in nanograms per milliliter and milligrams per liter. rCL_{urea}, renal urea clearance; AV, arteriovenous; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone.

Figure 7D). The association between ALP and mortality was not significantly modified by rCL_{urea} in the fully adjusted models ($P_{\text{interaction}}=0.53$). Trends in the adjusted association between ALP and mortality were consistent across rCL_{urea} strata (Figure 4, A–C), which was also supported in models using restricted cubic splines

(Supplemental Figure 6). When categorizing patients into 15 groups according to baseline levels of ALP and rCL_{urea}, higher rCL_{urea} was consistently associated with lower mortality risk across serum ALP categories (reference: ALP=60 to <80 U/L and rCL_{urea}≥3.0 ml/min per 1.73 m²; $P_{\text{trend}}<0.001$) (Figure 4D).

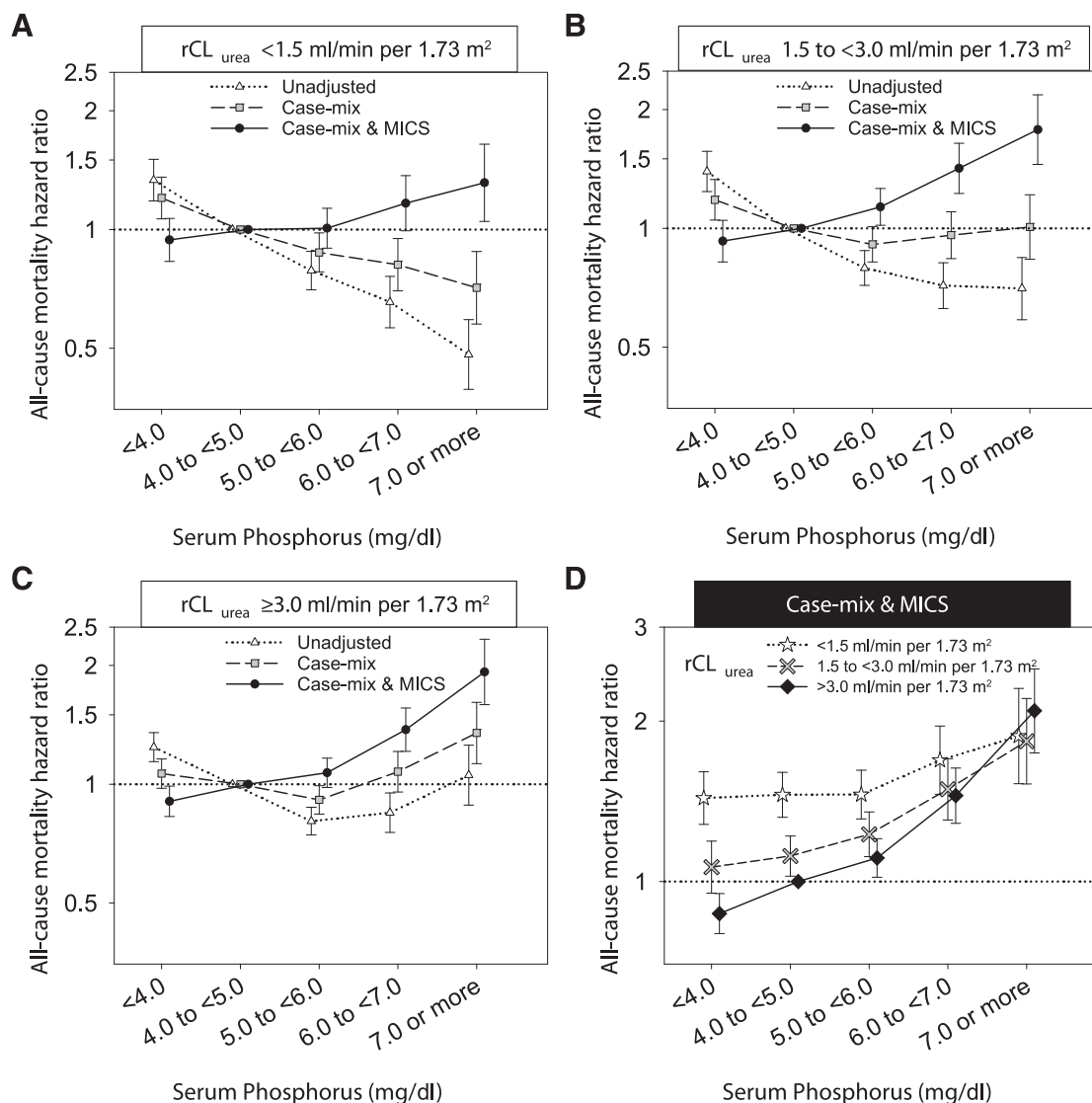


Figure 1. | Higher mortality risk associated with higher serum phosphorus was observed across the three strata of renal urea clearance (rCL_{urea}) but pronounced among patients with greater rCL_{urea} . Association of baseline serum phosphorus with all-cause mortality in 35,114 incident hemodialysis patients with baseline rCL_{urea} of (A) <1.5 , (B) 1.5 to <3.0 , and (C) ≥ 3.0 ml/min per 1.73 m^2 and (D) the mortality risk of 15 groups stratified by baseline rCL_{urea} and serum phosphorus in the case mix and malnutrition-inflammation cachexia syndrome (MICS) model (phosphorus of 4.0 to <5.0 mg/dl with $rCL_{urea} \geq 3.0$ ml/min per 1.73 m^2 as the reference).

Discussion

This study examined the modification of the association of several MBD parameters with mortality by RKF among incident hemodialysis patients and found several novel observations. RKF levels modified the association of phosphorus and intact PTH with all-cause death. The relative mortality risk associated with high serum phosphorus concentrations was stronger in patients with higher rCL_{urea} levels. As for serum intact PTH, lower concentrations showed a higher mortality risk among patients with low rCL_{urea} , whereas higher concentrations were associated with higher mortality among patients with high rCL_{urea} levels. In contrast, higher concentrations of calcium and ALP were associated with all-cause death irrespective of rCL_{urea} levels. Of note, higher rCL_{urea} was associated with better survival across MBD marker categories, with

the exception that patients with serum phosphorus ≥ 7.0 mg/dl showed comparable mortality risk irrespective of rCL_{urea} levels.

Mortality risk associated with high serum phosphorus concentrations was pronounced in the high rCL_{urea} group versus the low rCL_{urea} group. Serum phosphorus was lower among patients on hemodialysis with higher rCL_{urea} levels, which is consistent with the observation that RKF, even at such low levels, contributes to substantial clearance of phosphorus in patients with ESRD (23). High serum phosphorus levels among patients with high RKF may indicate nonadherence to diet, hemodialysis prescription, and/or medications, including phosphorus binders and cinacalcet, as well as high-turnover bone disease. High dietary phosphorus loading has been shown to induce inflammation, malnutrition, vascular calcification, and

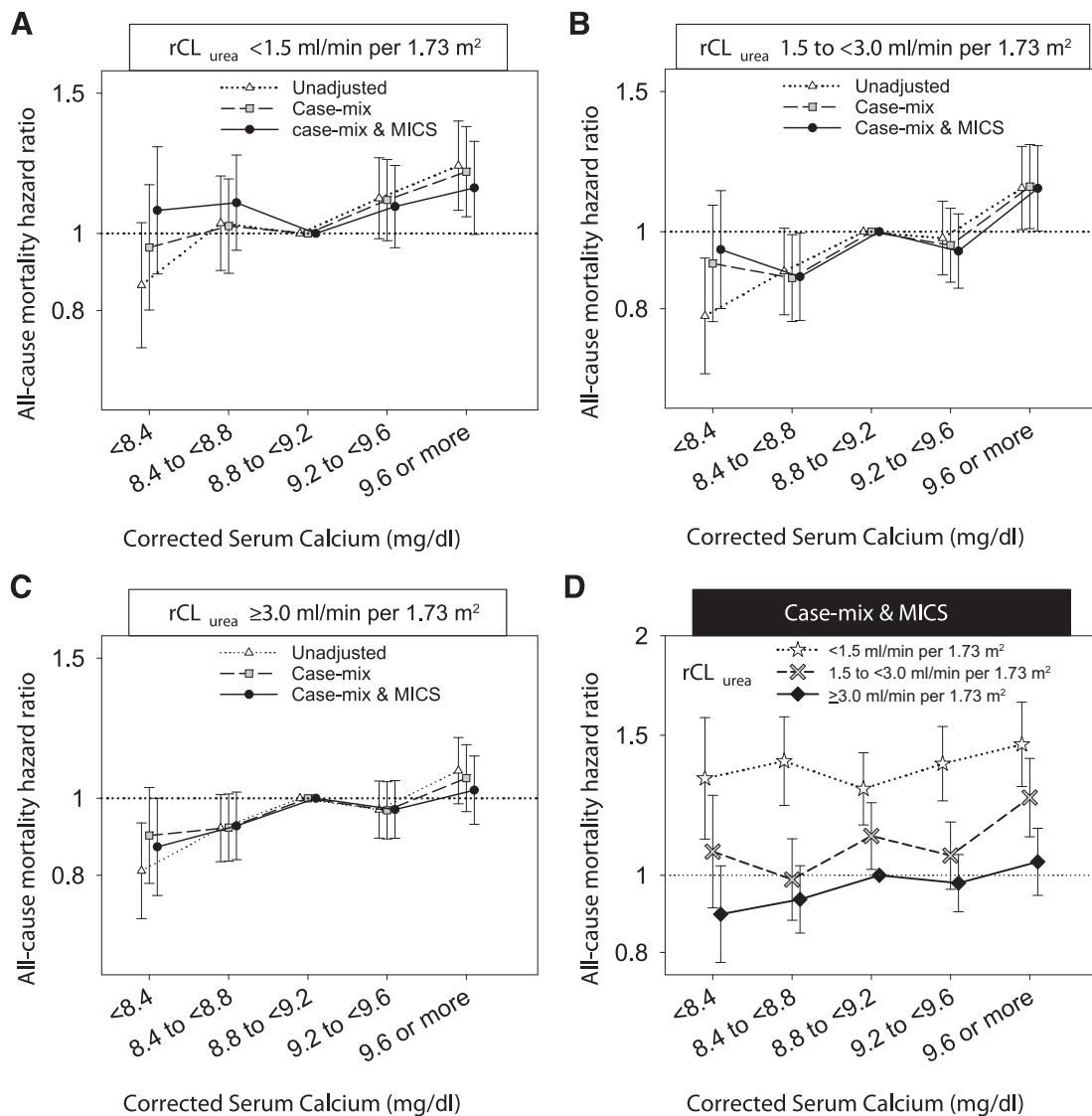


Figure 2. | The association between higher baseline albumin-corrected serum calcium and higher mortality was consistent across the three strata of renal urea clearance (rCL_{urea}). Association of baseline albumin-corrected serum calcium with all-cause mortality in 35,114 incident hemodialysis patients with baseline rCL_{urea} of (A) <1.5, (B) 1.5 to <3.0, and (C) ≥3.0 ml/min per 1.73 m² and (D) the mortality risk of 15 groups stratified by baseline rCL_{urea} and albumin-corrected calcium in the case mix and malnutrition-inflammation cachexia syndrome (MICS) model (albumin-corrected calcium of 8.8 to <9.2 mg/dl with rCL_{urea} ≥3.0 ml/min per 1.73 m² as the reference).

premature death in rodent CKD models (24,25), and nonuse of phosphorus binders has also been linked to higher mortality (26).

Previous studies have shown a U-shaped or linear association between serum calcium and mortality in patients on hemodialysis depending on the calcium categorizations, assays used, variables accounted for, statistical models, and the underlying study population (12,27–31). Our results also confirmed that higher serum calcium levels were associated with higher mortality risk in the overall analysis, which could be explained by several mechanisms, including vascular calcification, hypertension, and infection (32). Meanwhile, in contrast to the interaction between serum phosphorus and rCL_{urea}, the association of serum calcium with all-cause mortality was not significantly modified by rCL_{urea}. This finding may be explained by

the fact that calcium is less likely to be affected by RKF than phosphorus. Recent calcium balance studies have consistently shown that calcium loads resulted in little or no increase in urinary calcium excretion, even in patients with CKD stages 3 and 4 (33,34). Calcium may be excreted into the urine at even lower levels in patients with ESRD and low RKF, and indeed, we did not observe significant differences in albumin-corrected calcium across rCL_{urea} strata.

There have been mixed data on the PTH-mortality association in patients on hemodialysis (1), and these inconsistent findings may be explained by unmeasured or residual confounding by their RKF. Several-fold higher concentrations of intact PTH are required to maintain normal bone turnover among patients with ESRD (35), known as skeletal resistance to PTH (36). This phenomena

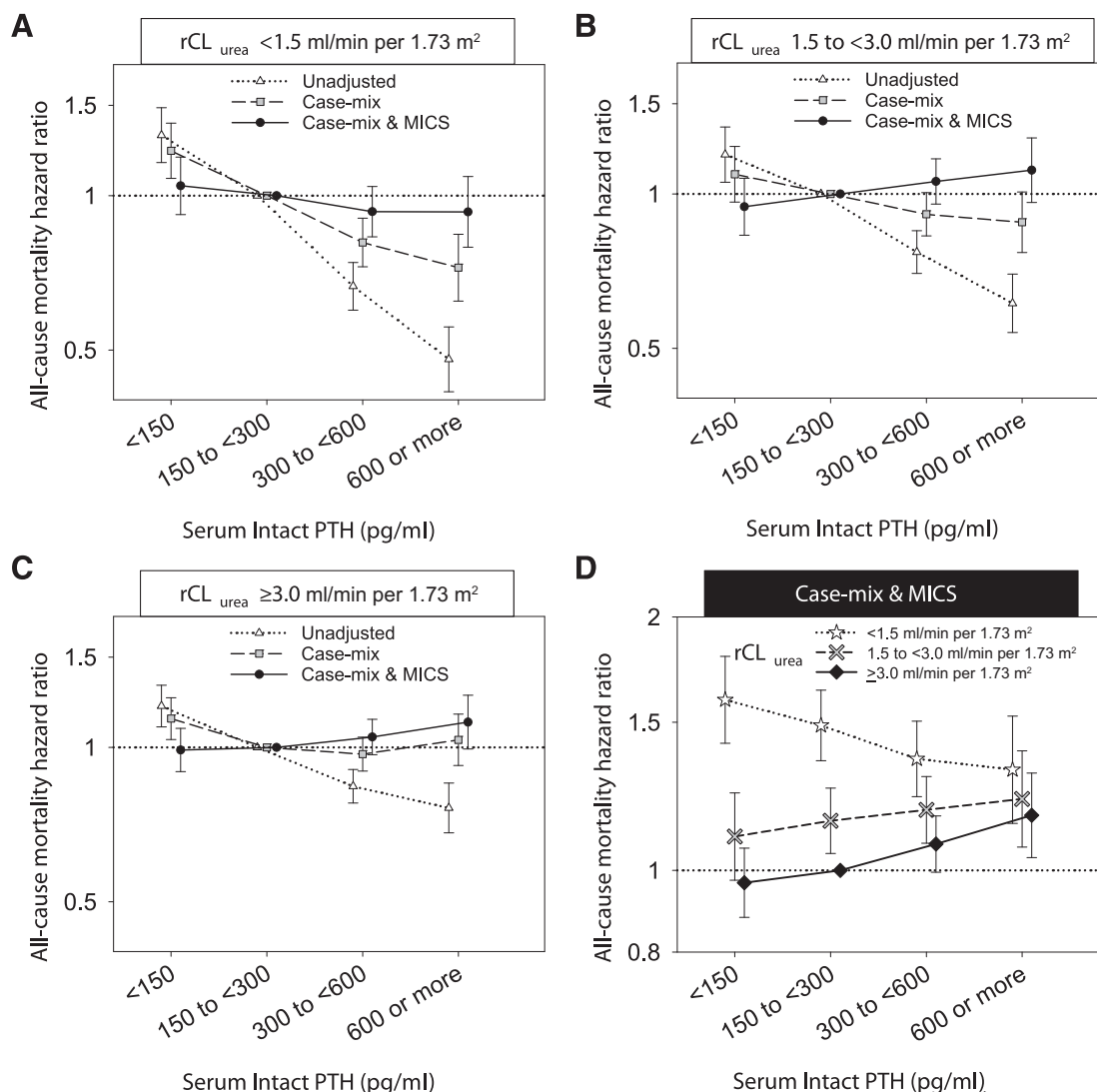


Figure 3. | Lower serum intact parathyroid hormone (PTH) showed a higher mortality risk among patients with low renal urea clearance (rCL_{urea}), whereas higher serum PTH was associated with higher mortality among patients with high rCL_{urea} . Association of baseline serum intact PTH with all-cause mortality in 35,114 incident hemodialysis patients with baseline rCL_{urea} of (A) <1.5 , (B) 1.5 to <3.0 , and (C) ≥ 3.0 and (D) the mortality risk of 12 groups stratified by baseline rCL_{urea} and serum intact PTH in the case mix and malnutrition-inflammation cachexia syndrome (MICS) model (intact PTH of 150 to <300 pg/ml with $rCL_{urea} \geq 3.0$ ml/min per 1.73 m² as the reference).

is partly due to the diminished PTH receptor expression of osteoblast in the uremic milieu (37,38). Also, accumulated bioinactive 7–84 PTH fragment in patients with ESRD interferes with the second generation intact PTH assay, resulting in falsely higher values of PTH (39). However, these abnormalities in the uremic milieu are likely to be less severe among patients with substantial RKF compared with those with little or no RKF (6,40–42). Our study showed for the first time that higher intact PTH levels were associated with lower mortality among patients on hemodialysis with low RKF, whereas higher intact PTH levels showed a higher mortality risk among patients with substantial RKF. Additionally, the effect of impaired capacity of the bone to buffer mineral loads due to low bone turnover may be accentuated among patients with little or no RKF, resulting in accelerated cardiovascular calcification (43,44). In contrast, we observed a consistent

association between higher ALP and higher mortality across rCL_{urea} levels. Although PTH affects bone metabolism, ALP is excreted from the bone and arteries with calcification (45), and hence, it is a useful marker of bone metabolism and active osteochondrogenesis (46–48).

Our results can be interpreted from the other viewpoint of the effect modification of the association between RKF levels and mortality by MBD parameters. The association of higher RKF with better survival was attenuated among patients with higher levels of phosphorus and intact PTH. Nevertheless, patients with greater RKF consistently showed better survival even after rigorous adjustment, supporting the recently highlighted importance of RKF in the hemodialysis population (6,20).

Strengths of our study include its large sample size of patients on hemodialysis with RKF data and use of uniform laboratory measurements. However, several limitations

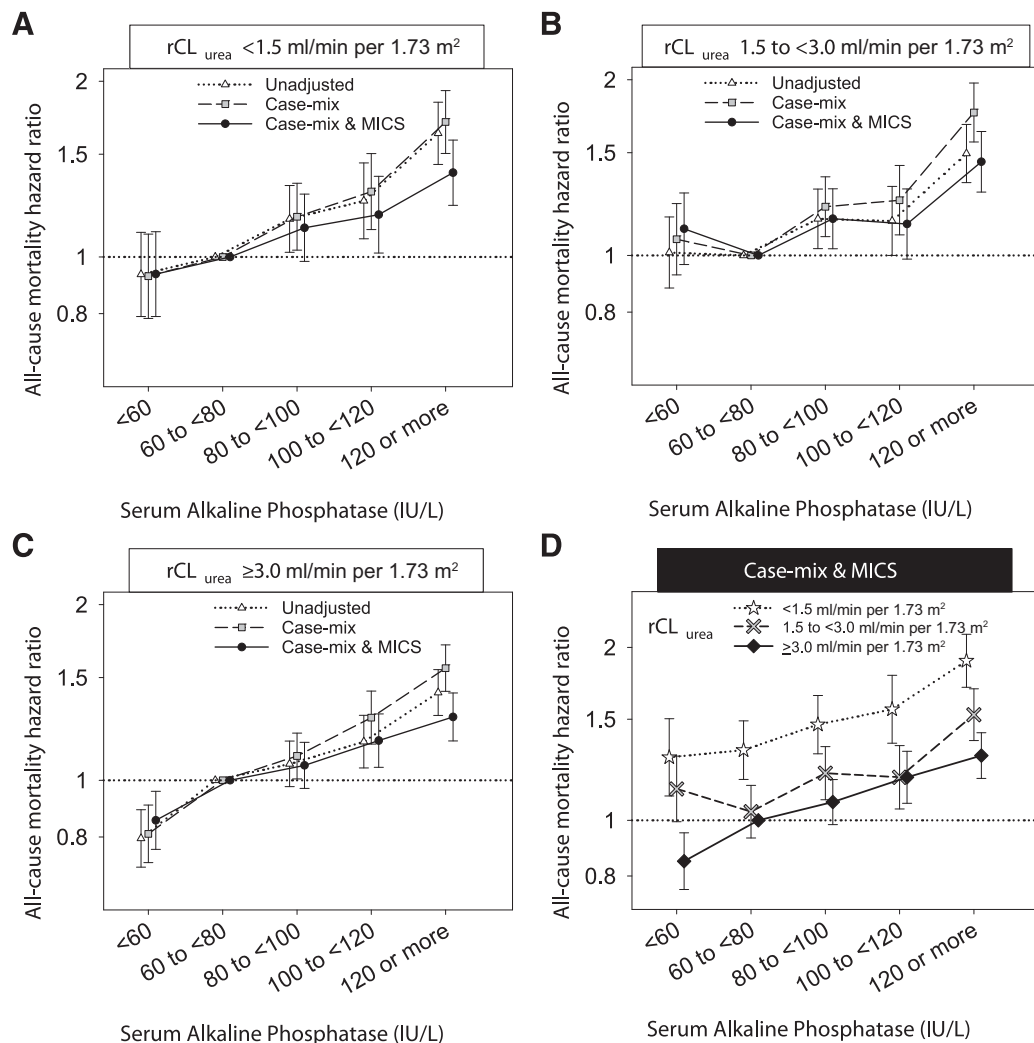


Figure 4. | The association between higher baseline alkaline phosphatase (ALP) and higher mortality was consistent across the three strata of renal urea clearance (rCL_{urea}). Association of baseline serum ALP with all-cause mortality in 35,114 incident hemodialysis patients with baseline rCL_{urea} of (A) < 1.5 , (B) 1.5 to < 3.0 , and (C) ≥ 3.0 ml/min per $1.73 m^2$ and (D) the mortality risk of 15 groups stratified by baseline rCL_{urea} and serum ALP in the case mix and malnutrition-inflammation cachexia syndrome (MICS) model (ALP of 60 to < 80 U/L with $rCL_{urea} \geq 3.0$ ml/min per $1.73 m^2$ as the reference).

should be noted. First, as with other observational studies, our study cannot prove causality. There may also be residual confounding or unmeasured confounders on the basis of vitamin D deficiency, inflammatory status, elevated fibroblast growth factor-23, treatment adherence, and inadequate predialysis care (49–54). Second, RKF may not be accurate given the use of rCL_{urea} , the difficulties in punctual and complete collection of urine samples, and the use of factor 0.9 for estimating average predialysis serum urea. Nevertheless, the population-level associations can be estimated from an adequate number of patients if such errors are not associated with the outcome, and a recent study has shown that change in rCL_{urea} used in this study was closely related to all-cause mortality (20). Third, the reason for urine being collected (or not collected) was not available in this administrative database, and potential selection bias may exist, because patients with limited RKF are less likely to have undergone urine collections.

However, similar patterns of association between all MBD markers and mortality were observed between included and excluded patients, suggesting the independence of the eligibility criteria of this study from those associations. Fourth, we included exclusively incident hemodialysis patients, and it is unclear whether our findings can be extrapolated to prevalent hemodialysis patients. Fifth, cause-specific death was not examined given a limited number of each event, even with, so far, the largest number of patients on hemodialysis with data on rCL_{urea} .

In conclusion, our study showed that RKF modified the association of serum phosphorus and intact PTH with all-cause mortality among incident hemodialysis patients, whereas serum calcium and ALP showed consistent associations with mortality irrespective of RKF. Future studies with a long-term follow-up period are needed to explain the underlying mechanisms of those associations and

examine whether taking account for RKF in the assessment of mortality risk associated with serum phosphorus and intact PTH improves patient management and clinical outcomes among patients on hemodialysis.

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